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Change in mammographic density across birth cohorts of Dutch breast cancer screening participants

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High mammographic density is a well-known risk factor for breast cancer. This study aimed to search for a possible birth cohort effect on mammographic density, which might contribute to explain the increasing breast cancer incidence. We separately analyzed left and right breast density of Dutch women from a 13-year period (2003–2016) in the breast cancer screening programme. First, we analyzed age-specific changes in average percent dense volume (PDV) across birth cohorts. A linear regression analysis (PDV *vs.* year of birth) indicated a small but statistically significant increase in women of: 1) age 50 and born from 1952 to 1966 (left, slope = 0.04, $p = 0.003$; right, slope = 0.09, $p < 0.0001$); 2) age 55 and born from 1948 to 1961 (right, slope = 0.04, $p = 0.01$); and 3) age 70 and born from 1933 to 1946 (right, slope = 0.05, $p = 0.002$). A decrease of total breast volume seemed to explain the increase in PDV. Second, we compared proportion of women with dense breast in women born in 1946–1953 and 1959–1966, and observed a statistical significant increase of proportion of highly dense breast in later born women, in the 51 to 55 age-groups for the left breast (around a 20% increase in each age-group), and in the 50 to 56 age-groups for the right breast (increase ranging from 27% to 48%). The study indicated a slight increase in mammography density across birth cohorts, most pronounced for women in their early 50s, and more marked for the right than for the left breast.

Background

With about one fourth of all cancer cases in women, breast cancer is the most common type of cancer and the leading cause of cancer death among women worldwide.[1] Many risk factors for breast cancer are known, including family history, age at menarche, age at menopause, and alcohol use (see Ref. 2 and references therein). Among these, one of the strongest risk factors is mammographic density (see Refs. 3,4 and references therein), i.e. a measure of the proportion of fibroglandular tissue among the total of fibroglandular and fat tissue in the breast.

Age is another key factor influencing the incidence of breast cancer, although not in a linear way.[5] Indeed, only about 7% of breast cancer cases occur before the age of 40 years,[6] and the incidence pattern of breast cancer follows a rather characteristic curve, with increasing incidence over age but with a less steep slope after menopause, producing the so-called *Clemmesen's hook*.[5]

In a recent pooled analysis,[7] the effect of aging and menopausal status on mammographic density was investigated, and the authors found density to decrease with increasing age, and to be lower in postmenopausal than in premenopausal women of the same age. A Danish study with repeated measurements for the same women over a 10-year period[8] indicated a birth cohort effect on density with an increase in the proportion of

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What's new?

Women with dense breast tissue are at increased risk of breast cancer. Here, changes in mammographic density were investigated across birth cohorts in women enrolled in a breast cancer screening program in the Netherlands. The findings reveal an increase in the average fraction of dense tissue in the breast across cohorts. In particular, greater breast density was observed in a higher proportion of women in later-born than earlier-born birth cohorts. The increase was most significant among women in their early 50s and may be linked to a reported shift toward older age at menopause among women in Europe.

women with mixed/dense mammographic density from women born in the 1920s to women born in the 1940s.

In our study, we analyzed mammographic data obtained during the Dutch breast cancer screening programme to investigate the possible presence of a birth cohort effect on mammographic density.

Materials and Methods

Data description and study population

We analyzed 3D volumetric breast measurements of the total breast volume and of the fibroglandular volume for the left and right breasts separately, automatically estimated from 2D digital mammograms (mostly mediolateral oblique (MLO) and few craniocaudal (CC) views) using the VolparaDensity software (version 1.5.0, Volpara Solutions, Wellington, New Zealand).[9]

Data were collected during a population-based breast cancer screening programme, in particular from the Preventicon screening unit in Utrecht, the Netherlands, of the Foundation of Population Screening Mid-West, where women aged 50–75 years were invited to screening every second year. Overall, our data covered a time span of 13 years, from September 2003 to September 2016. Digital mammograms were obtained using Lorad Selenia DM systems (Hologic, Danbury, Conn.).

In total, data derived from 69,041 Dutch women. Of these, 16,562 were screened once, 11,512 screened twice, 12,041 three times, 12,412 four times, 10,081 five times, 5,704 six times, 727 seven times, 2 eight times. Each screening/observation corresponded to both left and right breast measurement. Overall, 215,091 observations were included in our analysis. Of these, 1,004 measurements of the left breast and 1,366 of the right breast were missing. The presence of implants was the most frequent cause for missing values.

The observations included information on women aged 48–76 years at screening and born in the period 1929–1966. Years of birth were included only partially in the original dataset. Therefore, when missing, they were calculated as *min{year of screening – age at screening}*, where the minimum was taken over all the observations of the same woman. The heat map in Figure 1 provides an overview of the year of birth/age distribution.

Statistical analysis

First, we studied the time trend of the percent dense volume (*PDV = (fibroglandular volume)/(breast volume)*), separately for left and right breast, across consecutive birth cohorts for given age groups, namely women 50, 55, 60 and 70 years old. For the four age-groups, a linear regression model of the PDV against year of birth has been applied. Outcome measures are the slope of the regression line, the standard error, and the *p*-value for t-test, determining whether the slope differs significantly from zero. Similar analyses were made for the total breast volume and for fibroglandular tissue volume.

Second, we classified each single dense tissue measurements according to the Volpara Density Grade (VDG) 4th Edition (see e.g. Ref. 10), defined as follows:

$$\begin{aligned}
&\text{VDG} = 1 \text{ for } \quad 0\% \le \text{PDV} < 4.5\%,\\
&\text{VDG} = 2 \text{ for } 4.5\% \le \text{PDV} < 7.5\%,\\
&\text{VDG} = 3 \text{ for } 7.5\% \le \text{PDV} < 15.5\%,\\
&\text{VDG} = 4 \text{ for PDV} \ge 15.5\%.
\end{aligned}$$

The VDG categories are based on the BI-RADS density scale, and several previous studies have found a moderate or good agreement between them, see Refs. 11,12 and references therein.

As dense breast is a risk factor for breast cancer, one could hypothesize that the increasing trend in the breast cancer incidence rate[13] might be partially explained by an underlying increase of mammographic density. Therefore, we compared the proportions of women with VDG = 3 and VDG = 4, stratified by age, within two groups, namely women born in the years 1946–1953 and 1959–1966. The two periods corresponded to the 2nd and 4th quartile of the year of birth distribution (counted only once per woman), and were chosen in order to ensure overlap in age-groups and to use data of latest available birth cohorts (see Fig. 1). Relative risk (RR) with 95% confidence interval, obtained with unconditional maximum likelihood method, with small-sample adjustment, and corresponding chi-squared test *p*-values were calculated. Relative risk adjusted for small sample is defined as follows. Denoting by 0,1 the 1946–1953 and 1959–1966 groups, respectively, we have $RR = \frac{c_1/n_1}{(c_0+1)/(n_0+1)}$, where c_i, denotes the number of cases in the group i (e.g. c_1 = number of women with VDG = 4 in 1959–1966 group) and n_i the total number of women in the group i (e.g. n_0 = number of women in 1946–1953 group).

In our dataset, 63 women had been screened twice at the same age. For these women, we selected the observation with highest VDG, or the earliest observation when the VDG was the same, separately for left and right breast. Therefore, in this analysis each woman was correctly counted only once per age group. Missing values were excluded from the counting.

Statistical analyses were performed with R 3.5.0, using the Epitools package. All plots were created in R 3.5.0, with ggplot2, grid, gridExtra and gtable packages.

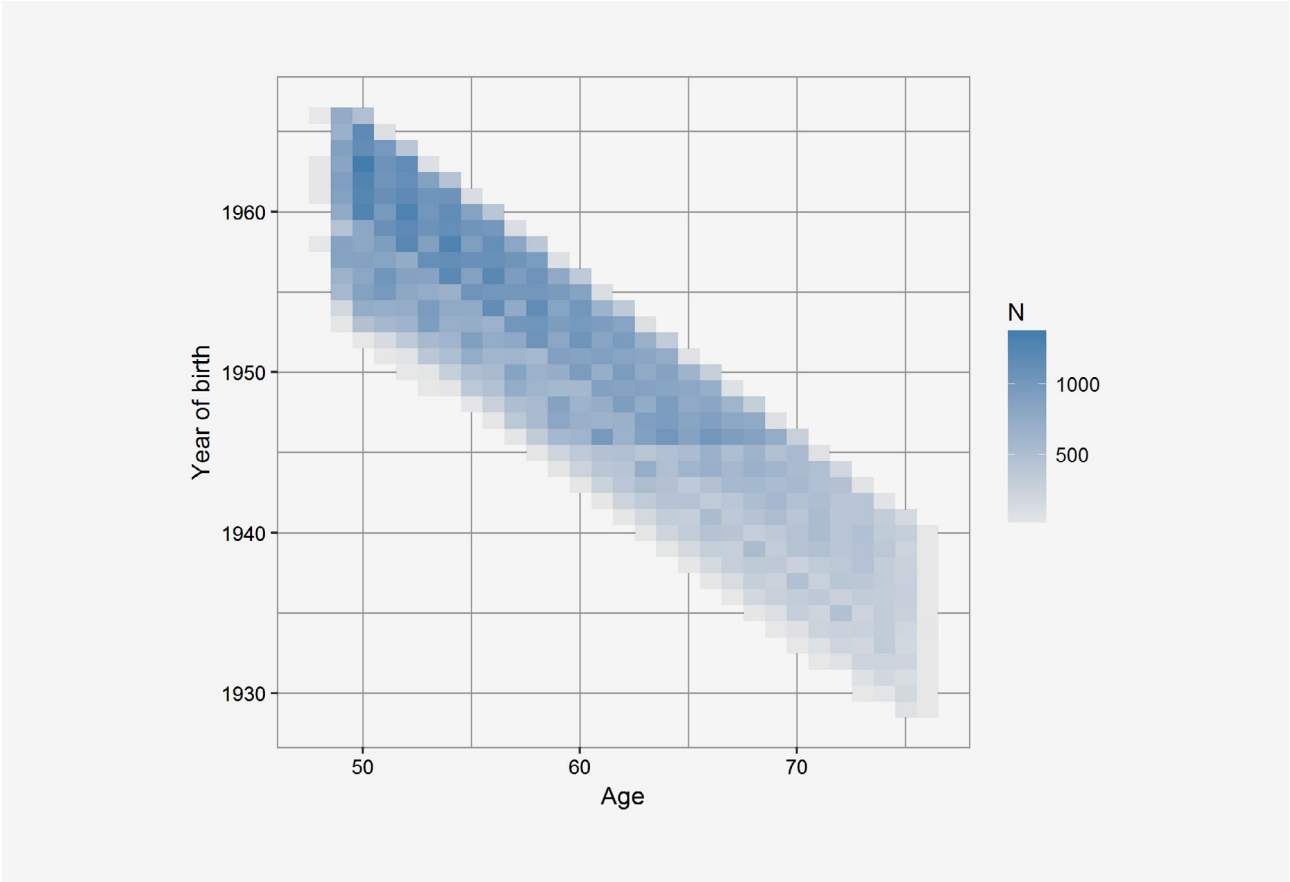

Figure 1. Heatmap of the number of observations (N) by age and year of birth. [Color figure can be viewed at wileyonlinelibrary.com]

Results

Trend in the proportion of dense tissue

Our data showed a strong age component in proportion of dense volume with an average percentage of dense volume being around 10% for women aged 50 years, and around 6% for women aged 70 years (Fig. 2.) The data did, however, also indicate an increase of the proportion of dense volume in later born as opposed to earlier born. Indeed, a linear regression model showed a statistically significant increase in different age groups, with quite remarkable differences between left and right breast (see Table 1 and Fig. 2). Namely, for the left breast we observed a statistically significant positive slope (Sl = 0.04, $p = 0.003$) in the 50 age group, whereas we found nonsignificant values in the other age-groups. Rather surprisingly, the increase of the proportion of the dense tissue emerged more clearly in the right breast. Indeed, the 50 and 70 age groups showed statistically significant positive regression slopes (Sl = 0.09 and $p < 0.0001$, Sl = 0.05 and $p = 0.002$, respectively), as well as the 55 age group, although with a p-value close to the significance threshold (Sl = 0.04 and $p = 0.01$). Furthermore, it was worth noticing that, in all age groups, the linear regression slope for the right breast was larger than the corresponding value for the left breast.

In order to better understand the possible cause of the observed trend in the PDV, we separately analyzed the trends of the total breast volume and in dense tissue volume (Table 1 and Fig. 2). Rather surprisingly, we found a sharp and statistically significant decline of the total breast volume in women aged 55 (Sl = −6.58, $p < 0.0001$ for the left breast, and Sl = −7.98, $p < 0.0001$ for the right breast) and 60 (Sl = −9.31, $p < 0.0001$ for the left breast, and Sl = −9.66, $p < 0.0001$ for the right breast). A smaller reduction was seen in the other age groups, although nonstatistically significant.

A similar pattern was observed for the dense tissue volume, however, with some important differences. Indeed, while for the 55 and 60 age groups the dense tissue volume mirrored the decline seen in the total breast volume (thus, resulting in the stable proportion between the dense and the fat tissue reflected in the PDV). In the 50 age group the dense tissue volume remained stable in the left breast (Sl = −0.07, $p = 0.47$) and increased slightly in the right breast (Sl = 0.21, $p = 0.03$) (thus, resulting in the slightly increasing PDV for the left breast and the more sharply increasing PDV for the right breast).

Once again, one could observe a different behavior between left and right breast, with the latter showing a more pronounced decline of the total breast volume and a less rapid decrease (or even an increase) of the dense tissue volume. This fact could therefore explain the observed differences in the increase of the percent dense volume between the left and the right breasts.

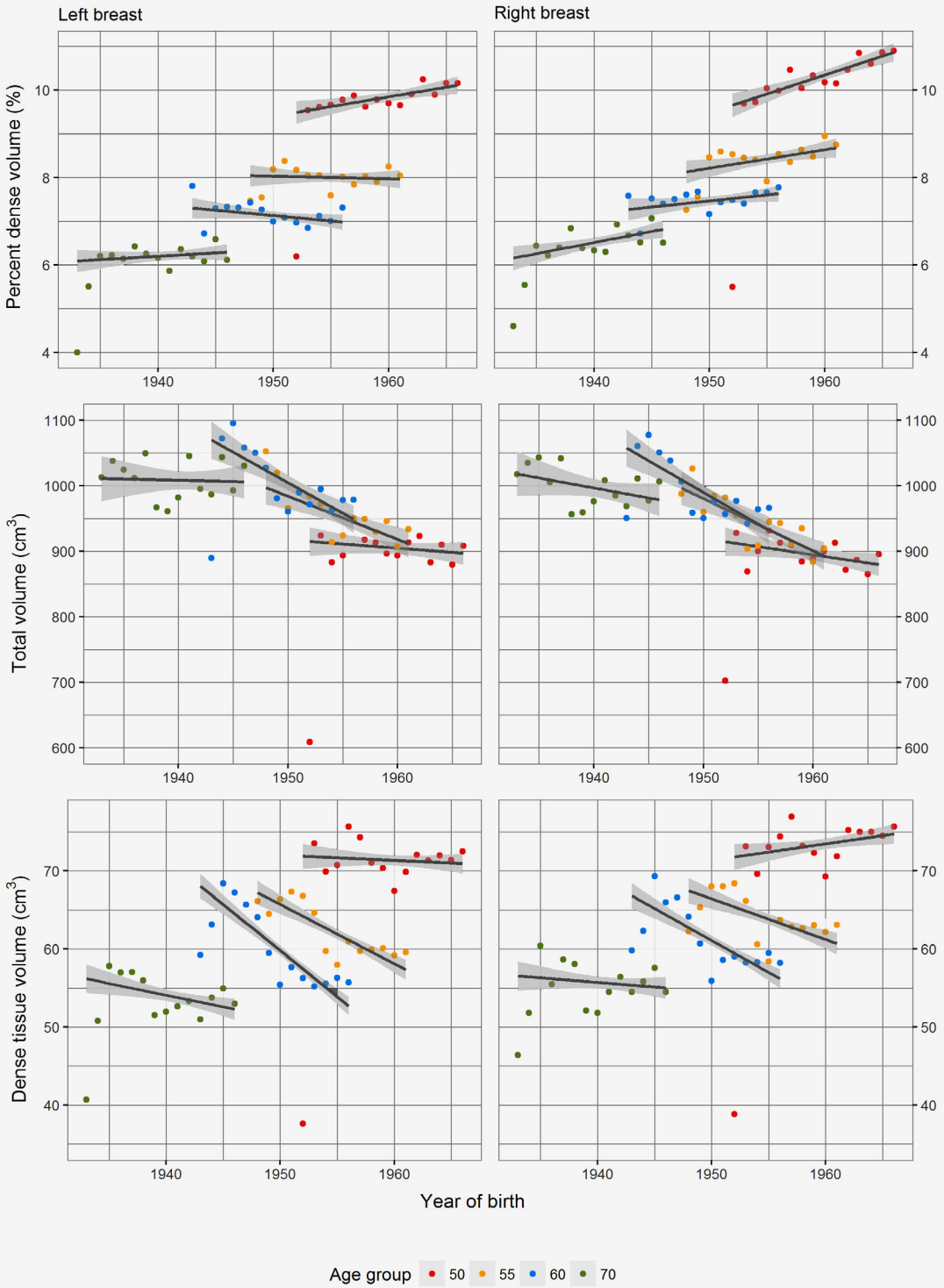

Figure 2. Mean (dots) of the percent dense volume, breast and dense tissue volume by age group and birth cohort, and regression lines with 95% confidence regions (shaded areas). [Color figure can be viewed at wileyonlinelibrary.com]

Proportion of women with high VDG

As a second analysis, we compared the proportion of women with the highest proportions of dense breast among those born in 1946–1953 and 1959–1966, stratifying by age. Results, namely proportion of women with VDG = 3 and VDG = 4, respectively, in each group, corresponding relative risk adjusted

Table 1. Slope (Sl), corresponding standard error (SE) and p-value of the regression lines in the four age-groups

Age group	50 years		55 years		60 years		70 years	
Birth cohorts	1952–1966		1948–1961		1943–1956		1933–1946	
	Left b.	Right b.	Left b.	Right b.	Left b.	Right b.	Left b.	Right b.
Percent dense volume								
Sl	0.04	0.09	−0.01	0.04	−0.02	0.03	0.02	0.05
SE	0.01	0.02	0.02	0.02	0.01	0.02	0.02	0.02
p-*value*	0.003	‹0.0001	0.71	0.01	0.09	0.07	0.31	0.002
Breast volume								
Sl	−1.28	−2.5	−6.58	−7.98	−9.31	−9.66	−0.39	−3.05
SE	1.26	1.27	1.66	1.65	1.73	1.73	2.08	2.05
p-*value*	0.31	0.05	‹0.0001	‹0.0001	‹0.0001	‹0.0001	0.85	0.13
Fibroglandular tissue volume								
Sl	−0.07	0.21	−0.76	−0.52	−1.18	−0.82	−0.30	−0.12
SE	0.09	0.10	0.10	0.11	0.10	0.10	0.11	0.11
p-*value*	0.47	0.03	‹0.0001	‹0.0001	‹0.0001	‹0.0001	0.007	0.30

for small-sample, confidence interval and *p*-value, are shown in Tables 2 and 3 and Figure 3. The age interval, 49–57 years, considered in our analysis corresponded to the subset of observations where data from both groups of birth cohorts were available.

The analysis showed that the proportion of women with VDG = 3 was nonstatistically significant different between the two groups (see Table 2). On the other hand, the proportion of women with highly dense breast (i.e., VDG = 4) was generally

Table 2. Proportion of women with VDG = 3, stratified by age, relative risk (1959–1966 vs. 1946–1953), 95% confidence interval and p-value

	Women born in 1946–1953		Women born in 1959–1966			
	Left breast	Right breast	Left breast	Right breast	Left breast	Right breast
Age	VDG = 3 / tot (%)	VDG = 3 / tot (%)	VDG = 3 / tot (%)	VDG = 3 / tot (%)	RR[1] (95% CI) *p*-value	RR[1] (95% CI) *p*-value
49	5 / 14 (35.7)	5 / 13 (38.5)	2,254 / 6,087 (37.0)	2,319 / 6,098 (38.0)	0.93 (0.46–1.87) $p = 0.9$	0.89 (0.45–1.77) $p = 0.97$
50	175 / 469 (37.3)	179 / 472 (37.9)	3,171 / 8,729 (36.3)	3,225 / 8,732 (36.9)	0.97 (0.86–1.09) $p = 0.7$	0.97 (0.86–1.09) $p = 0.7$
51	249 / 716 (34.8)	255 / 717 (35.6)	2,245 / 6,324 (35.5)	2,296 / 6,334 (36.2)	1.02 (0.92–1.13) $p = 0.7$	1.02 (0.92–1.13) $p = 0.7$
52	358 / 1,042 (34.4)	379 / 1,046 (36.2)	2,198 / 6,311 (34.8)	2,248 / 6,313 (35.6)	1.01 (0.92–1.11) $p = 0.8$	0.98 (0.90–1.07) $p = 0.7$
53	676 / 1907 (35.4)	696 /1908 (36.5)	1,333 /4064 (32.8)	1,420 / 4,081 (34.8)	0.92 (0.86–1.00) $p = 0.04$	0.95 (0.89–1.02) $p = 0.2$
54	723 / 2,124 (34.0)	755 /2129 (35.5)	1,215 / 3,760 (32.3)	1,311 / 3,785 (34.6)	0.95 (0.88–1.02) $p = 0.2$	0.98 (0.91–1.05) $p = 0.5$
55	1,029 / 3,254 (31.6)	1,058 / 3,253 (32.5)	591 / 1989 (29.7)	658 / 2006 (32.8)	0.94 (0.86–1.02) $p = 0.1$	1.01 (0.93–1.09) $p = 0.8$
56	1,029 / 3,313 (31.1)	1,095 / 3,317 (33.0)	434 / 1,399 (31.0)	454 / 1,403 (32.4)	1.00 (0.91–1.10) $p = 0.97$	0.98 (0.90–1.07) $p = 0.7$
57	1,508 / 4,914 (30.7)	1,541 / 4,917 (31.3)	36 / 110 (32.7)	35 / 109 (32.1)	1.07 (0.81–1.40) $p = 0.6$	1.02 (0.78–1.35) $p = 0.9$

[1]Small-sample adjusted.

Table 3. Proportion of women with VDG = 4, stratified by age, relative risk (1959–1966 vs. 1946–1953), 95% confidence interval and p-value

	Women born in 1946–1953		Women born in 1959–1966			
	Left breast	Right breast	Left breast	Right breast	Left breast	Right breast
Age	VDG = 4 / tot (%)	VDG = 4 / tot (%)	VDG = 4 / tot (%)	VDG = 4 / tot (%)	RR[1] (95% CI) *p*-value	RR[1] (95% CI) *p*-value
49	2 / 14 (14.3)	1 / 13 (7.7)	1,188 / 6,087 (19.5)	1,368 / 6,098 (22.4)	0.98 (0.27–3.52) $p = 0.6$	1.57 (0.24–10.33) $p = 0.2$
50	77 / 469 (16.4)	69 / 472 (14.6)	1,524 / 8,729 (17.5)	1,773 / 8,732 (20.3)	1.05 (0.85–1.30) $p = 0.6$	1.37 (1.10–1.71) $p = 0.003$
51	89 / 716 (12.4)	93 / 717 (13.0)	989 / 6,324 (15.6)	1,208 / 6,334 (19.1)	1.25 (1.02–1.53) $p = 0.02$	1.46 (1.20–1.77) $p < 0.001$
52	119 / 1,042 (11.4)	135 / 1,046 (13.0)	882 / 6,311 (14.0)	1,058 / 6,313 (16.8)	1.21 (1.01–1.45) $p = 0.02$	1.29 (1.09–1.52) $p = 0.002$
53	186 / 1907 (9.8)	197 /1908 (10.3)	502 /4064 (12.3)	625 / 4,081 (15.3)	1.26 (1.07–1.48) $p = 0.003$	1.48 (1.27–1.72) $p < 0.001$
54	190 / 2,124 (9.0)	213 /2129 (10.0)	411 / 3,760 (10.9)	484 / 3,785 (12.8)	1.22 (1.03–1.43) $p = 0.02$	1.27 (1.09–1.48) $p = 0.001$
55	269 / 3,254 (8.3)	317 / 3,253 (9.7)	204 / 1989 (10.3)	258 / 2006 (12.9)	1.24 (1.04–1.47) $p = 0.01$	1.32 (1.13–1.54) $p < 0.001$
56	248 / 3,313 (7.5)	283 / 3,317 (8.5)	128 / 1,399 (9.2)	163 / 1,403 (11.6)	1.22 (0.99–1.49) $p = 0.05$	1.36 (1.13–1.63) $p = 0.001$
57	305 / 4,914 (6.2)	377 / 4,917 (7.7)	11 / 110 (10.0)	10 / 109 (9.2)	1.61 (0.91–2.84) $p = 0.1$	1.19 (0.66–2.17) $p = 0.6$

[1]Small-sample adjusted.

higher for the later born women (group 1959–1966) compared to those born earlier (group 1946–1953), but again with some differences between left and right breasts (see Table 3). More specifically, for the left breast at the age of 53 years we observed a statistically significant 26% increase in the proportion of women with VDG = 4 for women born in 1959–1966 as compared to those born in 1946–1953. A similar increase appeared at ages 51, 52, 54 and 55, with similar values which were still statistically significant, but with *p*-values close to the significance threshold ($p = 0.02, 0.02, 0.02, 0.01$, respectively). For the right breast, we obtained a statistically significantly increased risk from the older to the younger birth cohort for all ages from 50 to 56, ranging from 27% up to 48%.

Discussion

Our study of mammographic data from the Dutch breast cancer screening programme indicated the presence of a possible birth cohort effect on mammographic density, in particular for women in their 50s, and more marked for the right than for the left breast.

Our time trend analysis indicated that a reduction of the average breast volume occurred across birth cohorts, and that changes in the dense tissue part did not follow the same behavior. Therefore, the observed increase of the PDV could be attributed both to the combination of a more rapid decline of the fat tissue volume than of the dense tissue volume (e.g. 50 age group, left breast), and to the combination of a decrease of the fat tissue volume with an increase of the dense tissue volume (e.g. 50 age group, right breast). Moreover, the asymmetric behavior between the two breasts could be seen also in the secular trends, where the decline in total breast volume seems to be most pronounced in the right breast, while the decline in the dense tissue volume looks more rapid in the left one.

In the analyzed dataset, we did not have individual data on breast cancer risk factors. Possible explanations of the observed patterns therefore have to be inferred for available population data. Users of hormone therapy have a higher mammographic density than nonusers.[14–18] The possible birth cohort effect on mammographic density observed in the earlier Danish study was seen for both users and nonusers of hormone therapy, but the density levels were considerably higher in the user than in the nonuser group.[8] The Dutch data analyzed in our study were derived from September 2003 to September 2016.

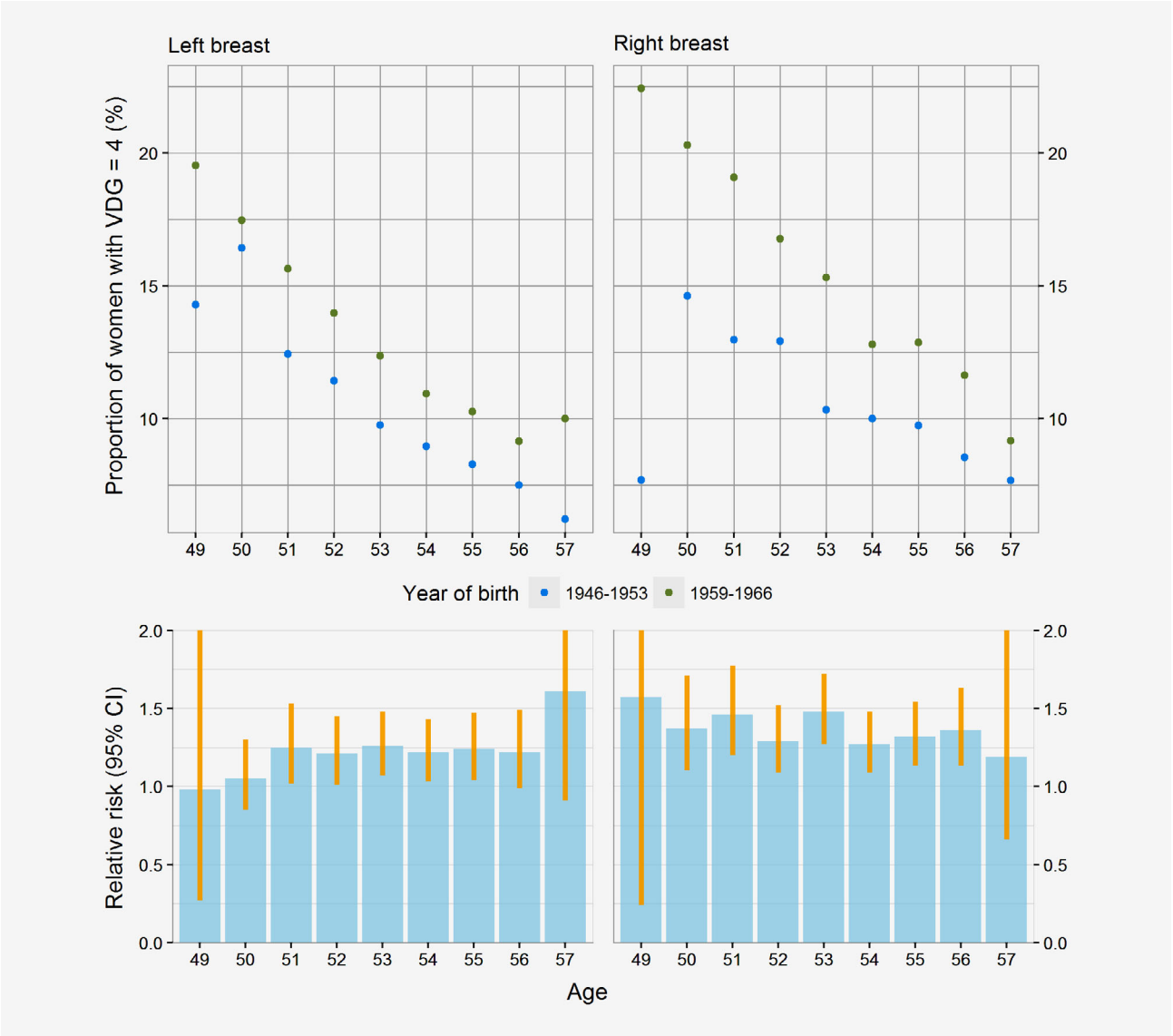

Figure 3. Upper plots: proportion of women with VDG = 4 (PDV ≥ 15.5%), by age group, in the birth cohorts 1946-1953 *vs.* 1959-1966. Lower plots: corresponding relative risk and 95% confidence interval. Note that, for the sake of readability, the upper endpoints of the confidence intervals for the 49 and 57 age groups are not included in the plots (cf. Table 3). [Color figure can be viewed at wileyonlinelibrary.com]

In the Netherlands, as in other high-income countries, the use of hormone therapy decreased,[19] following the publication of two landmark studies on the adverse effects of hormone therapy.[20,21] However, even before 2003 the use of hormone therapy was already infrequent in the Netherlands,[19] and by far the majority of the 50-year old Dutch women included in our study have lived through menopause and early menopausal age after the decline in use of hormone therapy. Hormone therapy is therefore unlikely to explain the increasing trend over birth cohorts in mammographic density for 50 years old women indicated in our data. Other possible causes of the observed trends could be changes in reproductive factors such as parity and younger age at first birth, known to be associated with lower mammographic density.[22–24]

The pooled analysis of cross-sectional mammographic density data from women from different countries and ethnic groups showed mammographic density (defined as dense area/breast area, these being read from 2D images) to be lower in postmenopausal than in premenopausal women of the same age.[7] Firm data on changes in menopausal age across birth cohorts are sparse. A number of studies do, however, indicate a shift toward older age of natural menopause in European women.[25–30] Such a shift could explain our finding of an increase in the average PDV among women in their 50s, but it is more difficult to see how this could relate to our finding of a decrease in the fatty volume. However, assuming that BMI correlates positively with breast volume, our finding of an increasing density related to an overall decrease of breast volume would

confirm the inverse association between density and BMI found in previous studies.[23,24]

Nonetheless, despite the lack of data on breast cancer incidence or hormonal therapy in our study population, our finding could contribute to explain, at least partially, the birth cohort effect on the increasing breast cancer incidence observed in the Netherlands[31] across the 1938–1962 birth cohorts, as well as in the UK,[32] Spain[33] and France.[34]

In our data, changes in mammographic density were more pronounced in the right breast than in the left breast. Although differences between left and right breasts are known and documented in literature (e.g. laterality of breast cancer[35,36]), to the best of our knowledge this is the first study indicating that the change in mammographic density is proceeding asymmetrically for the two breasts. Further studies are needed to investigate, and possibly confirm, such phenomenon.

On a parallel note, the results of our analysis on mammographic density seem to be in accordance with the well-known decrease of breast density with age, and they further suggest that this might be due to an absolute reduction of dense tissue volume (see Fig. 2). However, further statistical analyses are needed to confirm this.

Our study had both strengths and limitations. First, it was a strength that the data derived from a 13 year observation period from a population-based screening programme. Second, all data consist of objective, fully automated measurements, rather than determined by radiologists. Third, no change in the mammography technology took place during the data collection period and always the same version of the Volpara software was used for the extraction of the volume measurements.

Furthermore, our study differs from previously mentioned studies on mammographic density trends in two ways. First, our data included a longer observation period. Second, our data included more recent birth cohorts of women (born up to the 1960s).

The study had, however, also some limitations. Even though all data came from one screening unit, a change in the team of radiographers may have influenced mammography positioning and/or compression techniques. Another limitation was the lack of individual information on risk factors, such as childhood body mass index, height, parity and age at first birth, which are known to influence mammographic density.[37]

Finally, it is worth pointing out that the results of the time trend analyses of the breast measurements have to be interpreted carefully. Indeed, we did not in advance expect to find (and, as a matter of fact, we did not observe) a linear relation between those quantities and women's year of birth. Therefore, the linear regression used in the analysis is only meant to capture a general time trend behavior, which should be better analyzed with longer time series.

In conclusion, this study based on mammographic density measurements collected over a 13 year period in the Netherlands indicated that density increased over birth cohort in particular for women in their 50s. This could possibly be related to an increasing age of natural menopause, but further longitudinal studies are needed to test this observation.

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